REMARKS

Claim 2 has been amended. Support for the amendment can be found in the Specification as filed, for example, page 9, lines 9-11, page 12, line 26-page 13, line 4; page 20, lines 4-8; and page 25, lines 14-16. Therefore, no new matter has been introduced by this amendment. The following addresses the substance of the Office Action.

1. Title of the invention is descriptive

The current title of the application is: "Prevention of Diabetes through Induction of Immunological Tolerance". This title accurately reflects the claimed invention, and distinctly points out what is claimed in the application.

2. References in IDS not found in File

Applicant has resubmitted the references previously submitted in the parent application.

3. Compliance with the Written Description Requirement

The Examiner rejected Claims 2-9 under the written description requirement of 35 U.S.C. §112, first paragraph. The Examiner pointed out that the specification must describe the invention in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In accordance with the written description guidelines of MPEP 2163, "[p]ossession may be shown in a variety of ways including . . . by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention."

Here, the specification is quite clear in showing the distinguishing identifying characteristics of the subject matter of Claims 2-9. In particular, all of the features of Claim 2 are specifically described in the specification as filed at page 3, line 28 through page 4, line 19. Additional description of the specific features of these claims is set forth at page 4, lines 3-4; page 10, lines 12-16, and page 19, lines 1-14. One skilled in the art reviewing these portions of the specification would have no doubt that the Applicants had possession of the invention. Therefore, Applicant asserts that Claims 2-9 are supported in the Specification as filed and are in compliance with 35 U.S.C. §112, first paragraph.

4. Compliance with the Enablement Requirement

The Examiner believes that the specification does not reasonably provide enablement for a method of preventing onset of Type I diabetes in a mammal comprising implanting insulin-

producing cells encapsulated in a biologically compatible membrane. The reasons the Examiner stated for the rejection are: **A)** unpredictability of the prevention of diabetes in human from the murine data; **B)** need for screening for susceptible individuals; **C)** need for undue experimentation to determine screening and testing protocols to demonstrate the efficacy of the claimed invention. Each of these reasons is addressed below:

A. Reasonable predictability of the prevention of diabetes in human from *in vivo* data obtained in NOD mice.

As discussed above in connection with compliance with the written description requirement, the specification describes every feature of the claimed invention. One skilled in the art would have no difficulty carrying out the steps for making and using the invention based on this description. To establish that one actually carrying out these steps could successfully achieve the claimed result, i.e. prevention of diabetes, Applicant submitted a Declaration of David Scharp showing that NOD mice receiving the treatment described in the specification were prevented from becoming diabetic. Nevertheless, the Examiner is questioning the value of such evidence based on alleged lack of predictability of the prevention of diabetes in human from *in vivo* data obtained in the NOD mice.

However, the Examiner is setting forth a much stricter standard than required by law. MPEP 2107.03 establishes the following:

> Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. Thus, an applicant may provide data generated using a particular animal model with an appropriate explanation as to why that data supports the asserted utility. The absence of a certification that the test in question is an industry-accepted model is not dispositive of whether data from an animal model is in fact relevant to the asserted utility. Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility."

In the present case, the animal tests submitted by Applicant have been established as reasonably predictive by those skilled in the art. The NOD (non-obese diabetic) mouse is the standard animal model for conducting research on Type I diabetes and other autoimmune disease. The NIH recognize the NOD mouse as the model animal for diabetes and maintains a research colony and data base on these animals for researchers. The NIH state "The NOD mouse, which

spontaneously develops type 1 diabetes, is a valuable animal model that is used extensively in research exploring the etiology, prevention, and treatment of this disease. It is a vital research tool for testing promising prevention and treatment strategies at the preclinical level." (http://www.niaid.nih.gov/dait/NODmice.htm, copy attached herein).

Moreover, Hanninen et al. (2003 "Development of new strategies to prevent type I diabetes: the role of animal models" *Annals of Medicine* **35**:546-563, copy attached herein) states: "The non-obese diabetic (NOD) mouse is the most widely used animal model of T1DM. [...] research in non-obese diabetic mice has led to the discovery of new strategies of diabetes prevention that are now in human clinical trials". The authors further present a whole list of current clinical trials based on strategies developed in NOD mice.

Additionally, the US PTO has also previously accepted the predictability of the results of prevention of diabetes in NOD mice and allowed claims to a method of protecting against the development of autoimmune diabetes in a susceptible subject (USP 6,841,152).

In addition, the Second Declaration of David Scharp under 37 CFR 1.132 submitted herewith states that the NOD mouse is the only animal model for human autoimmune, Type I diabetes because it is the only available model reasonably predictive of human disease. The same Declaration also shows that using the "one to two orders of magnitude" criteria for calculating the dose for tolerizing the experimental animals was successful in preventing the autoimmune disease under study – Type I diabetes. The NOD mice were implanted with 50 to 150 islets, which resulted in prevention of diabetes in these animals.

While it is true that questions have been raised whether the NOD model is absolutely predictive of treatment of humans, such an absolute correlation with human disease is not required to support enablement. MPEP 2107.03 further provides:

> The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use.

Therefore, using the proper standard set forth in the MPEP, the evidence provided by Applicant clearly supports that one skilled in the art would accept the NOD model as reasonably correlating to the condition in human.

B. Screening for susceptible individuals is well-known and routine

The Examiner also objected to the enablement provided by the specification based on an alleged failure to disclose how to screen for susceptible individuals. However, the specification as filed on page 19, lines 9-12, provides information that "in diabetes, the use of immune marker autoantibodies to establish preclinical diabetes has been well studied" The specification cites Palmer, *Diabetes Rev.* **1**(1):104-116, 1993 in support of this statement. In addition, Applicant provides herewith several references to support the position that screening for individuals susceptible to developing type I diabetes has been well-established in the art at the time the invention was made: Bonifacio et al. 1995 "Islet autoantibody markers in IDDM: risk assessment strategies yielding high sensitivity", *Diabetologia* **38**:816-22; Lee et al. 1995 "Relationships among 64k autoantibodies, pancreatic beta-cell function, HLA-DR antigens and HLA-DQ genes in patients with insulin-dependent diabetes mellitus in Korea", *Korean J. Intern. Med.* **10**:1-9; Bingley et al. 1994 "Combined analysis of autoantibodies improves prediction of IDDM in islet cell antibody-positive relatives", *Diabetes* **43**:1304-10; Zimmet et al. 1994 "Autoantibodies to glutamic acid decarboxylase and insulin in islet cell antibody positive presymptomatic type 1 diabetes mellitus: frequency and segregation by age and gender", *Diabet Med.* **11**:866-71; Christie et al. 1994 "Antibodies to islet 37k antigen, but not to glutamate decarboxylase, discriminate rapid progression to IDDM in endocrine autoimmunity", *Diabetes* **43**:1254-9; Tuomilehto et al. 1994 "Antibodies to glutamic acid decarboxylase as predictors of insulin-dependent diabetes mellitus before clinical onset of disease", *Lancet* **343**:1383-5; Zimmet et al. 1994 "Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency", *Diabet Med.* **11**:299-303, copies of which are submitted herewith.

"The specification need not disclose what is well known in the art." *See, e.g., In re Buchner,* 18 USPQ2d 1331 (Fed. Cir. 1991). Thus, there was no requirement for Applicants' specification to contain a thorough description of the well known techniques that were well-established as of the effective filing date. Accordingly, one skilled in the art would have no difficulty identifying suitable subjects for the treatment of the present invention.

C. Experimentation to determine screening and testing protocols to demonstrate the efficacy of the claimed invention in not undue

The Examiner also believed that undue experimentation would be required to determine screening and testing protocols. However, as established in both Declarations of David Scharp, M.D., testing protocols have already been established with minimum difficulty. As apparent from the claim, the goal of the invention is to prevent diabetes, i.e. maintain normoglycemia. Methods for determining whether normoglycemia is present have been exceedingly well known for many years; thus, only routine blood glucose monitoring would be required to demonstrate the efficacy of the claimed invention.

MPEP 2164.01(c) establishes that in order to meet the enablement requirement, one skilled in the art need only be able to discern an appropriate dosage or method of use without undue experimentation based on knowledge of compounds having similar physiological or biological activity. Here, the Specification at page 12, lines 26-30 clearly indicates that a dose of implanted insulin-producing cells to induce tolerance is one or two orders of magnitude less than a full dose of implant which provides adequate insulin production for normoglycemia. The full dose for achieving normoglycemia has been well worked out for many years. Accordingly, no difficulty would be had in obtaining the correct dose for any given individual. Accordingly, no undue experimentation would be required to practice the claimed invention.

5. Compliance with 35 U.S.C. 102

The Examiner rejected Claims 2-5, 7-9 as anticipated by US Patent 6,703,017 or by US Patent 5,425,764. In order to anticipate, the reference must teach each and every element of the claim. The '017 patent describes implanting insulin-producing cells in a dose of about 8,000-12,000 islets/kg of patient's body weight (col. 14, lines 7-9) to create a pancreas-like structure in a human patient. Therefore the implant in USP '017 is designed to treat diabetes by creating a live "insulin pump" in the body. Furthermore, Example 12 of USP '017 describes implanting 5,000 islets per NOD mouse which has developed diabetes (this dose equals 200,000 islet/kg of body weight), which resulted in normoglycemia in these animals. The '017 patent does not teach implanting a dose of insulin-producing cells encapsulated in a biologically-compatible membrane prior to onset of Type I diabetes, wherein said dose is at least one order of magnitude less than that necessary to achieve normoglycemia in a mammal of the same species with type I diabetes. The "017 patent only concerns itself with treating diabetes once established with

implanting islets, not preventing diabetes from becoming established by implanting a small, sub-therapeutic dose of encapsulated cells. Therefore, Claim 2 as currently amended, as well as claims dependent on Claim 2 are not anticipated by US Patent 6,703,017.

US Patent 5,425,764 describes a method of using an implantable bioartificial pancreas device containing insulin-secreting islets, to supply an exogenous source of insulin to treat the symptoms of diabetes. Accordingly, the '764 patent requires implantation of a curative dose of insulin-secreting cells, i.e. the dose necessary to achieve normoglycemia. As such the '764 Patent does not teach implanting a dose of insulin-producing cells encapsulated in a biologically-compatible membrane prior to onset of Type I diabetes, wherein said dose is at least one order of magnitude less than that necessary to achieve normoglycemia in a mammal of the same species with type I diabetes. The '764 patent is focused on a therapy for diabetes by implanting a large quantity of islets, and does not consider preventing diabetes from occurring by implanting a small dose of encapsulated islets. Therefore, Claim 2 as currently amended as well as claims dependent on Claim 2 are not anticipated by the '764 Patent.

Thus, Claims 2-5, 7-9 are in compliance with 35 U.S.C. § 102.

6. Compliance with 35 U.S.C. 103(a)

The Examiner rejected Claims 2-9 under 35 U.S.C. 103(a) as unpatentable over US Patent 6,703,017 or by US Patent 5,425764 in view of US Patent 5,529,914. However, pursuant to MPEP 2143, in order to establish a *prima facie* case of obviousness three requirements must be met: First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In the case of the present invention, the cited references fail to suggest all of the claim limitations. The novelty of Claims 2-9 over US Patent 6,703,017 and US Patent 5,425,764 is discussed above. As discussed above, neither of these patents teaches, or even suggests, a method involving implantation of a sub-curative dose of insulin-secreting cells. US Patent 5,529,914 discloses a method of encapsulating cells, but it fails to cure the deficiencies of US

Patent 6,703,017 and US Patent 5,425764. Therefore, Claims 2-9 are in compliance with 35 USC §103(a).

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

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Dated: April 29, 2005

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